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Therapeutic Review
Leukotriene Modifiers

Overview/Summary

The leukotriene modifiers (LTMs) are a class of medications used for long-term symptom control in patients with asthma as well as allergic rhinitis. The LTMs can be divided into two pharmacologic categories: leukotriene-receptor antagonists (LTRAs) and 5-lipoxygenase inhibitors. The LTRAs, which include montelukast and zafirlukast, exert their pharmacologic action by blocking the leukotriene receptor, thereby inhibiting the action of cysteinyl leukotrienes.[1,2] Cysteinyl leukotrienes play an important role in the pathophysiology of asthma and contribute to bronchoconstriction, increased airway responsiveness, mucous secretion, and the recruitment of inflammatory cells.[3] Blocking the action of cysteinyl leukotrienes has been shown to reduce or prevent airway obstruction and decrease the activation of inflammatory cells.[3] The only 5-lipoxygenase inhibitor currently available is zileuton. This agent inhibits the actions of the 5-lipoxygenase enzyme thereby preventing the formation of leukotrienes.[4] LTRAs and 5-lipoxygenase inhibitors elicit similar biologic responses in asthmatic patients, but differ in dosing requirements, adverse reactions, drug interactions, and pharmacokinetic parameters.[1,2,4] In February of 2008, the manufacturer of zileuton, Critical Therapeutics Inc. announced the discontinuation of their immediate release formulation. The currently available formulation is zileuton controlled release (CR).[5] Currently, none of these agents are available as generic formulations.

The medications presented in this review are all Food and Drug Administration (FDA)-approved for prophylaxis and chronic treatment of asthma. One of the LTMs, montelukast, has three additional FDA-approved indications for the treatment of symptoms of seasonal and perennial allergic rhinitis and for the prevention of exercise-induced bronchoconstriction.[1]

On March 27th, 2008 the FDA announced it was reviewing safety data regarding concerns about the possible association between the use of montelukast and suicidal ideations or behavior. The FDA requested that the manufactures of all three LTM agents submit adverse event data relating to suicidality mood, and behavioral adverse events. The most current information regarding these adverse events was released by the FDA on January 13th, 2009. The data reported that the leukotriene inhibitors do not appear to be associated with either suicide or suicidal behavior; however the studies examined were not designed to specifically measure these psychiatric conditions and the occurrence of underreporting is possible. The FDA is continuing to review data and has not yet reached a definitive conclusion regarding these agents and their potential to cause other psychiatric problems, such as mood and behavioral changes.[6-7]

Treatment guidelines published by the National, Heart, Lung, Blood Institute (NHLBI) recommend the use of inhaled corticosteroids (ICS) as first-line therapy for long-term control of persistent asthma symptoms in children and adults. In individuals over the age of 12, a long-acting β_2-agonist (LABA) used concurrently with either a low- or medium-dose ICS is preferred for the treatment of moderate persistent asthma. All three LTMs can be used as alternative adjunctive agents to low- and medium-dose ICS; however they are not recommended as preferred agents. Zileuton has not been studied in patients less than 12 years of age and either LTRA agent is preferred over it due to its limited efficacy data and the need for liver function monitoring. In children 5 to 11 years of age a LTRA is an alternative to low-dose ICS monotherapy. Additionally a low-dose ICS concurrently with a LABA or LTRA or medium-dose ICS monotherapy are all considered preferred options. LTRAs are also considered alternative agents in pediatric patients with severe asthma.[8] In children ages 0-4 years old montelukast is specifically

recommended as an alternative to a low-dose ICS and as an adjunctive option alongside the LABA agents with a medium and high-dose ICS in the more severe asthma stages.[8]

The Global Initiative for Asthma (GINA) guidelines recommend that LTMs can be used as alternative agents to low-dose ICSs. The LTMs are particularly appropriate in patients who are unable or unwilling to use ICSs, or in those who experience intolerable adverse events on ICS therapy. The LTM agents are also recommended as add-on treatment to medium- or high-dose ICS agents; however the benefit reported with this treatment combination has been shown to be less than that of a combination ICS and LABA.[9]

The Joint Task Force on Practice Parameters for Allergy and Immunology recommend that intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis and all are considered equally efficacious. They also suggest that intranasal antihistamines can also be considered as first-line treatment for both allergic and nonallergic rhinitis. The LTRAs alone or in combination with antihistamines are effective in the treatment of allergic rhinitis.[10]

The Institute for Clinical Systems Improvement (ICSI) guidelines notes that intranasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms. Antihistamines and cromolyn can be considered alternatives in patients who prefer not to use intranasal corticosteroids. Antihistamines are somewhat less effective than intranasal corticosteroids; however oral antihistamines are an effective alternative in patients who cannot use or prefer not to use intranasal corticosteroids. Moreover, LTMs are as effective as second-generation antihistamines for the treatment of allergic rhinitis; however they are not as effective as intranasal corticosteroids.[11]

It should be noted that neither the asthma nor the allergic rhinitis guidelines recommend one LTM over another.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Montelukast (Singulair®)	Leukotriene receptor antagonist	-
Zafirlukast (Accolate®)	Leukotriene receptor antagonist	-
Zileuton (Zyflo® CR)	5-lipoxygenase Inhibitor	-

CR=controlled release.

Indications

Table 2. Food and Drug Administration Approved Indications[1,2,4]

Generic Name	Prophylaxis and Chronic Treatment of Asthma	Prophylaxis of Exercise-Induced Bronchoconstriction	Symptoms of Seasonal Allergic Rhinitis	Symptoms of Perennial Allergic Rhinitis
Montelukast	✔	✔	✔	✔
Zafirlukast	✔			
Zileuton	✔			

Although not Food and Drug Administration (FDA)-approved both montelukast and zafirlukast have been used for the treatment of atopic dermatitis and urtacaria. Montelukast has additionally been used for the treatment of aspirin-induced asthma, eosinophilic gastroenteritis, and in migraine prophylaxis. Zafirlukast has been used for the treatment of exercise-induced asthma.[5]

Pharmacokinetics

Table 3. Pharmacokinetics[1,2,4,5]

Generic Name	Onset (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Montelukast	3-4	24	0	Unspecified	2.7-5.0
Zafirlukast	0.5	12	10	No	8-16
Zileuton	0.5-2.0	5-8	94.5	Yes	3.2

Clinical Trials

There are numerous placebo controlled trials examining the efficacy of the leukotriene modifiers (LTMs) for asthma as well as allergic rhinitis. There is also a large body of clinical data comparing the LTMs to inhaled corticosteroids (ICSs), and long-acting β_2-agonists (LABA). However the availability of head-to-head trials specifically comparing the LTMs is lacking.

When compared to placebo, LTMs demonstrated efficacy in most aspects of asthma control, including pulmonary function, asthma symptoms, β_2-agonist use, asthma exacerbations, and nighttime symptom control.[12-30]

When compared to other long-term controller medications, such as ICSs and LABAs, the LTMs have not demonstrated equivalence or significant advantages in clinical outcomes.

With regards to allergic rhinitis, montelukast has been shown to be more effective than placebo, and has demonstrated comparable efficacy to second-generation antihistamines; however it has not been shown to be as effective as intranasal corticosteroids.[31-35]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Asthma				
Knorr et al[12] Montelukast 5 mg chewable tablet every night at bedtime vs placebo	DB, MC, PC, RCT Children 6-14 years with an FEV_1 between 50%-85% of expected value, 15% or better reversibility after inhaled β_2-agonist therapy, daytime asthma symptoms that met a minimal value, and reported daily β_2-agonist use	N=336 8 weeks	Primary: Improvements in morning FEV_1 from baseline Secondary: Daytime asthma symptoms, morning and evening PEF, daily use of inhaled SABAs, nocturnal awakenings, pediatric asthma-specific quality of life questionnaire, global evaluations, changes in blood eosinophil count, school absences, asthma exacerbations, use of oral corticosteroids, discontinuations due to worsening of asthma, asthma control days	Primary: A significant improvement in percent change from baseline in FEV_1 was reported in patients in the montelukast group compared to the placebo group ($P<0.001$). Secondary: A significant improvement in daily use of β_2-agonists was observed in the montelukast group ($P=0.01$). Significant improvements in percentage of days and percentage of patients experiencing asthma exacerbations were reported in the montelukast group ($P=0.049$). A significant improvement in the pediatric asthma-specific quality of life questionnaire was noted in the montelukast group (symptoms; $P=0.007$, activity; $P=0.001$, emotions; $P=0.002$). A significant improvement in parental ($P=0.049$) and combined ($P=0.04$) global evaluations were observed in the montelukast group. A significant improvement in morning clinic-measured PEF was reported in the montelukast group ($P=0.03$). A significant decrease in blood eosinophil levels over 8 weeks was observed in the montelukast group ($P=0.02$). Other secondary endpoints did not reach statistical significance because the study was not powered appropriately to detect a difference.
Reiss et al[13] Montelukast 10 mg tablet every evening vs	DB, MC, PC, PG, RCT Patients 15-79 years with chronic stable asthma, FEV_1 50%-85% predicted value,	N=681 12 weeks	Primary: FEV_1 percent change from baseline and daytime asthma symptom score	Primary: A significant improvement in percent change from baseline in FEV_1 was reported in patients in the montelukast group ($P<0.001$). Secondary: A significant improvement in morning and evening PEF was reported in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo every evening Patients could also use ICSs during study.	15% or better improvement of FEV_1 after β_2-agonist, minimum level of daytime asthma symptoms, and use of an inhaled β_2-agonist		Secondary: Morning and evening PEF, daily use of inhaled SABAs, number of nocturnal awakenings per week, asthma- specific quality of life, global assessment, blood eosinophil count, percentage of days with asthma exacerbation, use of oral corticosteroids, discontinuation due to worsening of asthma, and asthma control days	the montelukast group (P<0.001). A significant improvement in daytime asthma symptoms and β_2-agonist use was observed in the montelukast group (P<0.001). Improvement in nocturnal awakenings was observed in the montelukast group (P value not reported). A significant improvement in asthma specific quality of life questionnaire was reported in the montelukast group ($P \leq 0.001$). A significant improvement in global assessments was observed in the montelukast group (P<0.001). A significant improvement in days without asthma exacerbations and days with asthma control was reported in the montelukast group (P<0.001). A significant improvement in blood eosinophil count was observed in the montelukast group (P<0.001). Remainder of secondary endpoints (use of oral corticosteroids and discontinuation due to worsening of asthma) were not significantly different between the montelukast group and the placebo group.
Suissa et al[14] Zafirlukast 20 mg tablet twice daily vs placebo twice daily	DB, MC, PC, RCT Patients 12 years or older, non-smokers in the last 6 months, smoking history of less than 10 pack-years, FEV_1 at least 55% of predicted value, with bronchial hyperresponsiveness and who were	N=146 13 weeks	Primary: Days without limitation of activity, days without use of β_2-agonists, days without episodes of asthma, days without sleep disturbance Secondary: Unscheduled health care visits and contacts, total number	Primary: Significantly more days without asthma symptoms was observed in the zafirlukast group (P=0.03). Significantly more days without β_2-agonist use were observed in the zafirlukast group (P=0.001). Significantly more days without episodes of asthma were reported in the zafirlukast group (P=0.003). More days without sleep disturbances were reported in the zafirlukast group (P>0.2).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	symptomatic during the 7 day run-in period of the study		of β_2-agonist inhalers used, number of prescriptions for non-asthma medications consumed, number of days absent from work or school	Secondary: A significant decrease in health care contacts was reported in the zafirlukast group (*P*=0.007). A significant decrease in asthma-related absenteeism was reported in zafirlukast group (*P*=0.04). A decrease in canisters of β_2-agonists used was observed in the zafirlukast group (*P*=0.17). A decrease in the use of non-asthma medications was observed in the zafirlukast group (*P*>0.2).
Israel et al[15] Zileuton 600 mg four times a day vs zileuton 800 mg twice a day vs placebo	DB, PC, RCT Patients 18-65 years with FEV_1 40%-75% of predicted value, a 15% or greater increase in FEV_1 30 minutes after inhalation of albuterol, and who were not being treated with inhaled or oral corticosteroids	N=139 4 weeks	Primary: FEV_1, asthma symptoms, and frequency of β_2-agonist use Secondary: Not reported	Primary: There was a significant (14.6%) increase in FEV_1 within 1 hour in both zileuton groups compared to baseline (*P*<0.001). There was a significant change in FEV_1 in the zileuton 600 mg group after 4 weeks compared to placebo (*P*=0.02). There was a significant decrease in asthma symptoms in all 3 groups (*P*<0.01), but the change was the greatest in the zileuton 600 mg group compared to placebo (*P*=0.02). There was a significant decrease in β_2-agonist use in the zileuton 600 and 800 mg group (*P*<0.001 and *P*=0.005 respectively) from baseline. Compared to placebo, the change was only significant in the zileuton 600 mg group (*P*=0.03). Secondary: Not reported
Israel et al[16] Zileuton 600 mg four times a day vs	DB, PG, RCT Patients with mild to moderate asthma, FEV_1 40%-80% of predicted value, only	N=401 13 weeks	Primary: Frequency of asthma exacerbations requiring corticosteroid treatment, use of inhaled β_2-agonists,	Primary: There was a significantly lower percentage of patients requiring corticosteroid treatment in the zileuton 600 mg group compared to placebo (*P*=0.02). There was a significant increase in FEV_1 in the zileuton 600 mg group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
zileuton 400 mg four times a day vs placebo	being treated with inhaled β_2-agonists		FEV_1, asthma symptoms, and quality of life evaluations Secondary: Not reported	compared to placebo (*P*=0.006). There was a significant improvement in quality of life assessments in the zileuton group compared to the placebo group (*P*=0.007). Secondary: Not reported
Nelson et al[17] Zileuton CR 600 mg twice a day vs zileuton IR 600 mg four times a day vs placebo CR or placebo IR Study consisted of a 2 week single blind placebo lead-in period between the CR and IR zileuton formulation and a 2 week run out period during which no study drug was taken.	AC, DB, MC, PC, RCT, Patients ≥12 years with moderate persistent asthma with an FEV_1 of 40%-75% of predicted when taken ≥48 hours after the last theophylline use and at least 6 hours after SABA use or 24 hours after LABA use who had not been hospitalized for asthma within 6 months; patients also had no history of elevated ALT levels 5 times the ULN or greater	N=591 16 weeks	Primary: Change from baseline in morning trough FEV_1 Secondary: Percentage of patients with clinically significant improvement in lung function (≥12% in FEV_1), change from baseline in morning PEFR, reduction in the number of daily puffs of SABA, safety	Primary: At week 12 compared with the placebo CR group the zileuton CR group demonstrated a significant mean improvement in FEV_1 (0.39 L [20.8%] vs 0.27 L [12.7%]; *P*=0.02). Compared to the placebo IR group the zileuton IR group reported a non significant improvement (0.38 L [19.3%] vs 0.28 L [14.1%]; *P*=0.19). Secondary: At week 12, 63.2% of the zileuton CR patients showed a 12.0% or greater improvement in FEV_1, compared to 50.0% in the placebo CR group. In the zileuton IR group 45.5% of patients had a 12.0% or great FEV_1 improvement, compared with 27.8% in the placebo IR group (*P*=0.02). However this was only seen in the IR group at week 4. The zileuton CR group reported an increasing mean improvement from baseline morning PEFR from 19.42 L/min for days 2-22 to 58.45 L/min for days 72-92. The difference between the zileuton CR group and the placebo CR group were not significant (*P* value not reported). Similar improvements were reported in the zileuton IR treatment group however the values were also not statistically significant. There was a 15.14% reduction from baseline of SABA use in the zileuton CR treatment grouped compared to a 2.29% reduction in the zileuton IR treatment group. The difference between the two groups was significant (*P*=0.009). The overall incidence of adverse events in the study was similar between all treatment groups (78.4% with zileuton CR, 76.8% with zileuton IR, and 77.3% with placebo IR).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The most common adverse events in the zileuton CR group were: exacerbation of asthma, headache, sinusitis, nausea, nasopharyngitis, and pharyngolaryngeal pain. Eight percent more patients in the placebo CR treatment group experienced asthma exacerbation that the zileuton CR group. Five out of 199 patients (2.5%) in the zileuton CR group and 1 out of 198 patients (0.5%) in the placebo CR group developed ALT level elevations of 3 times the ULN or greater. The investigators did not attribute the adverse events to the treatment medication. Two of the 97 patients (2.1%) in the zileuton IR group and 1 of the 97 patients (1.0%) in the placebo IR group developed ALT levels of 3 times the ULN or greater.
Wenzel et al[18] Zileuton 1,200 mg twice daily plus usual care vs placebo plus usual care	MC, PC, RCT Patients ≥12 years of age, with moderate persistent asthma, with an FEV_1 of ≥40% of predicted when taken at least 48 hours after the last theophylline use, at least 12 hours after the last salmeterol use, and had a ≥15% increase in FEV_1 at least 15 minutes after inhaled albuterol; patients also had no history of elevated ALT ≥5 time the ULN	N=926 6 month	Primary: Proportion of patients who experienced an ALT elevation of ≥3 times the ULN Secondary: FEV_1, morning and evening PEF, albuterol utilization, hospitalizations, change in quality of life test	Primary: The overall rate of adverse events were similar between the two groups (86.9% in the zileuton group and 84.7% in the placebo group reported at least one adverse event). The most common adverse events reported in the zileuton group were: exacerbation of asthma (33.1%), headache (23.4%), and nasopharyngitis (10.5%). The most common adverse events reported in the placebo group were: exacerbation of asthma (37.8%), headache (20.8%), nasopharyngitis (10.7%), and back pain (10.1%). A total of 13 patients in the study experienced an ALT elevation of ≥3 times the ULN. Of these patients 11 were in the zileuton CR group and 2 in the placebo group. Ten of the 11 cases were characteristic of pure hepatocellular injury. Secondary: Mean changes in FEV_1 were 0.17 L for zileuton CR and 0.13 L for the placebo group (*P*=0.260). Mean increase in morning PEF was 55.41 L/min in the zileuton CR treatment group, compared to 30.38 L/min in the placebo group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P=0.002). The mean increase in evening PEF was 38.98 L/min in the zileuton CR group, compared to 21.83 L/min in the placebo group (*P*=0.031). The number of albuterol puffs per day and occasions for use, was slightly reduced in both treatment groups, however the results were not significant (*P* values not reported). Sixteen patients in the zileuton group and 10 in the placebo group required an emergency room visit (*P*=0.408). The overall asthma quality of life score improved by 0.71 in the zileuton group and by 0.57 in the placebo group (*P*=0.083).
Szefler et al[19] Montelukast 5-10 mg daily (based on age) vs fluticasone propionate 100 µg twice daily There was no placebo washout between each treatment period so the first 4 weeks of each period served as the washout and were not included in the final analysis.	MC, RCT, XO Children 6-17 years old with mild to moderate persistent asthma, absence of corticosteroid use in previous 4 weeks, absence of LTMs in previous 2 weeks, absence of respiratory tract infection in previous 4 weeks, asthma symptoms or rescue bronchodilator use on average ≥3 days per week for past 4 weeks, reversibility defined as ≥12% improvement in FEV_1 after maximum bronchodilation or 20% improvement in FEV_1	N=144 16 weeks	Primary: Percent change in pre-bronchodilator FEV_1 from baseline Secondary: Not reported	Primary: A significantly greater percent change in FEV_1 from baseline in the fluticasone group was reported compared to the montelukast group (*P*<0.001). Seventeen percent of patients responded to both treatments, 23% responded to fluticasone alone, 5% responded to montelukast alone, and 55% responded to neither medication. Children with low pulmonary function or high levels of markers associated with allergic inflammation responded better to ICS than to montelukast. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	after methacholine dose of ≤12.5 mg/mL, and FEV_1 70% of predicted value or greater			
Zeiger et al[20] Montelukast 5-10 mg daily (based on age) vs fluticasone propionate 100 µg twice daily This is additional data from the previous study by Szefler et al[19].	MC, RCT, XO See Szefler et al[19]	N=144 16 weeks	Primary: Asthma control days Secondary: Pulmonary function as measured by eNO, FEV_1 and FEV_1/FVC, resistance of the respiratory system at 5 Hz, and area of reactance	Primary: Significant improvements in asthma control days were reported compared to baseline in both groups (*P*<0.001). A significant improvement in asthma control days in the fluticasone group was reported compared to the montelukast group (*P*<0.001). Secondary: A significant decrease in eNO in both groups was reported compared to baseline (*P*<0.001), and the difference between groups was significant, favoring fluticasone (*P*=0.028). Significant improvements were noted in both groups in FEV_1, FEV_1/FVC, resistance of the respiratory system at 5 Hz, and area of reactance compared to baseline.
Garcia et al[20] Montelukast 5 mg daily vs fluticasone propionate 100 µg twice daily	DB, NI, RCT Children 6-14 years old with mild persistent asthma (as defined by the Global Initiative for Asthma Executive Committee guidelines), FEV_1≥80% predicted value with β_2-agonist withheld ≥6 hours at least twice in run in period, and FEV_1 or PEF≥70% predicted value at visit 3	N=994 12 month	Primary: Percent of asthma rescue-free days measured as change from baseline Secondary: Percentage change from baseline in predicted FEV_1, percentage of patients requiring anti-asthma medications other than β_2-agonists, percentage of patients with an asthma attack,	Primary: Montelukast was shown to be equivalent to fluticasone in percentage of asthma rescue-free days. Secondary: A significant difference in change from baseline in percentage of predicted FEV_1 favoring fluticasone was observed (*P*=0.04). No significant difference in change from baseline in FEV_1 between the fluticasone group and montelukast group was observed. There was a significant difference in percentage of β_2-agonist use from baseline in both groups (*P*≤0.001). A significant decrease in percentage of β_2-agonist use in the fluticasone group was reported compared to the montelukast group (*P*=0.003).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			average percentage of days with β_2-agonist use, change in blood eosinophil count, patient reports of asthma control, patient lost school days, and parental lost work days	Significantly fewer patients in the fluticasone group used rescue asthma medications, other than β_2-agonists, compared to the montelukast group (*P* value not reported). Significantly fewer patients in the fluticasone group experienced an asthma attack compared to the montelukast group (*P* value not reported). There was no significant difference in the proportion of patients experiencing an asthma attack between the fluticasone group and montelukast group when analyzing only the patients who received no systemic corticosteroids during the previous year (*P* value not reported). A significant improvement in overall quality of life from baseline in both fluticasone and montelukast groups was reported ($P \leq 0.001$). A significant decrease in blood eosinophil count was reported in both fluticasone and montelukast groups from baseline ($P \leq 0.001$). There was a significant improvement in patient asthma control from baseline in both the fluticasone and montelukast groups ($P \leq 0.001$) though between-group comparison favored fluticasone (*P* value not reported). The proportion of patients with ≥1 lost school day during the 4 weeks preceding the 12 month visit was 8.8% in the montelukast group and 6.2% in the fluticasone group. The percentage of patients who lost >3 school days was 1.9% in the montelukast group and 2.1% in the fluticasone group. A ≥1 lost work day was reported in parents of 2.9% of montelukast patients and 2.0% of fluticasone patients during the 4 weeks prior to the 12 month visit, and the percentage whose parents lost >3 work days were reported as 0.4% in the montelukast group and 0.2% in the fluticasone group. The significance of these differences was not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Busse et al[21] Montelukast 10 mg daily vs fluticasone propionate 44 µg twice a day	DB, DD, PG, RCT Patients 15-83 years diagnosed with asthma for at least 6 months, pre-bronchodilator FEV_1 between 50%-80% of predicted value, increase in FEV_1 of 15% or greater after β_2-agonist use, regular or as-needed use of inhaled or oral β_2-agonist in the 3 months prior to screening	N=533 24 weeks	Primary: Mean percentage change from baseline in morning pre-medication FEV_1 Secondary: Mean change in FVC, $FEF_{25\%-75\%}$, morning and evening PEF, percentage of symptom-free days, asthma symptom scores, nighttime awakenings, daily rescue albuterol use, percentage of rescue-free days, physicians' global assessment of effectiveness, asthma quality of life questionnaire, patient-rated satisfaction with treatment	Primary: A significantly greater improvement in FEV_1 in the fluticasone group was reported compared to the montelukast group ($P \leq 0.002$). Secondary: A significantly greater improvement in all spirometric values in the fluticasone group was reported compared to the montelukast group ($P \leq 0.002$). A significant improvement in asthma symptom-free days in the fluticasone group was reported compared to montelukast group ($P<0.001$). A significant improvement in asthma symptom scores in the fluticasone group was observed compared to the montelukast group ($P<0.001$). A significant improvement in nighttime awakenings in the fluticasone group was observed compared to the montelukast group ($P=0.023$). A significant improvement in rescue albuterol use in the fluticasone group was observed compared to the montelukast group ($P<0.001$). The physician's global assessment significantly favored fluticasone compared to montelukast ($P<0.001$). Significantly greater improvements noted on the asthma quality of life questionnaire in the fluticasone group compared to the montelukast group ($P \leq 0.001$). Patient-rated satisfaction with treatment significantly favored the fluticasone group compared to the montelukast group ($P<0.001$).
Yildirim et al[22] Montelukast 10 mg daily and budesonide 400 µg	PG, RCT Patients (mean age 36.93±2.98 years) who had moderate	N=30 6 weeks	Primary: Morning, daytime, and evening asthma symptoms, morning and evening PEF,	Primary: A significant decrease in morning and daytime symptom scores was reported in both groups compared to baseline scores ($P<0.05$), but no significant differences between the two groups were noted.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily (administered as separate entities) vs budesonide 800 µg daily	persistent asthma for minimum of 6 months and were admitted into the Department of Chest Diseases in Trabzon, Turkey between March and December of 2000		FEV_1, blood eosinophil counts, frequency of SABA use, frequency of asthma exacerbations Secondary: Not reported	No significant difference in evening symptom scores was reported in either group compared to baseline. No significant differences in FEV_1 or PEF values from baseline or between groups were reported. A significant decrease in blood eosinophil counts in both groups when compared to baseline ($P<0.05$) was reported but there was no significant difference between the two groups. There was a significant decrease in beta-agonist use in the budesonide plus montelukast group compared to baseline ($P<0.05$), but there was no significant difference in β_2-agonist use in the high-dose budesonide group compared to baseline. No patients in either group experienced an asthma exacerbation during the study period. Secondary: Not reported
Price et al[23] Montelukast 10 mg daily and budesonide MDI 800 µg daily (administered as separate entities) vs budesonide MDI 1,600 µg daily	DB, NI, PG, RCT Patients 15-75 years old diagnosed with asthma for more than 1 year not optimally controlled on regular ICS; patients were non-smokers or ex-smokers, FEV_1 values of $\geq$50% of predicted value at visits 1 and 3, $\geq$12% improvement in FEV_1 after β_2-agonist treatment of at least 1 puff per day during the	N=889 12 weeks	Primary: Morning PEF values Secondary: Initial treatment effect on PEF (days 1-3), daily self-reported β_2-agonist use, daytime symptoms, nocturnal awakenings, asthma exacerbations, asthma-free days, blood eosinophil counts, asthma specific quality of life	Primary: A significant improvement in morning PEF compared to baseline for both groups was reported ($P<0.001$) but differences between groups were insignificant at the end of the study. Secondary: The change from baseline in PEF during the first 3 days of treatment was significantly more rapid in the montelukast plus budesonide group compared to the budesonide group alone ($P<0.001$). All other secondary endpoints were not significantly different from baseline or between groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	last 2 weeks of the run in period			
Fish et al[24] Montelukast 10 mg daily vs salmeterol xinafoate 50 µg twice a day	DB, DD, MC, PG, RCT Patients ≥15 years of age diagnosed with asthma remaining symptomatic despite therapy with a stable dose of ICS for the previous 30 days	N=948 12 weeks	Primary: Morning PEF values Secondary: Evening PEF, daytime asthma symptom score, supplemental albuterol use, nighttime awakenings	Primary: Significant increases in morning PEF in the salmeterol group were observed compared to the montelukast group (P<0.001). Secondary: A significant decrease in symptom scores in the salmeterol group was reported compared to the montelukast group (P=0.039). A significant decrease in supplemental albuterol use in the salmeterol group was reported compared to the montelukast group (P≤0.012). Significantly greater reductions in nighttime awakenings in the salmeterol group were reported compared to the montelukast group (P=0.015).
Bjermer et al[25] Montelukast 10 mg daily and fluticasone 100 µg twice a day (administered as separate entities) vs fluticasone 100 µg twice a day and salmeterol 50 µg twice a day (administered as separate entities)	DB, DD, MC, PG, RCT Patients 15-72 years old with chronic asthma ≥1 year, baseline FEV_1 50%-90% predicted value, improvement of 12% or more in FEV_1 or in morning PEF after β_2-agonist use, regular use of ICS for at least 8 weeks prior to study, average β_2-agonist use of at least 1 puff per day	N=1,490 52 weeks	Primary: Percentage of patients with at least one asthma exacerbation Secondary: Asthma specific quality of life, nocturnal awakenings, mean FEV_1 before and after β_2-agonist use, mean morning PEF, time to first asthma exacerbation, blood eosinophil counts	Primary: No significant difference between the 2 groups in percentage of patients with at least 1 asthma attack was reported. Secondary: A significant improvement in asthma specific quality of life compared to baseline in both groups was reported (P≤0.001), though there was no significant difference between the 2 groups. A significant decrease in nocturnal awakenings from baseline in both groups was reported (P≤0.001), though there was no significant difference between the 2 groups. A significant improvement in FEV_1 before β_2-agonist use in the salmeterol and fluticasone group was observed compared to the montelukast and fluticasone group (P≤0.001), though the improvement in FEV_1 after β_2-agonist use was similar between the 2 groups. A significantly larger increase in morning PEF in the salmeterol and fluticasone group was reported compared to the montelukast and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				fluticasone group ($P \leq 0.001$), though both groups significantly improved morning PEF values from baseline ($P \leq 0.001$). No significant differences between the groups regarding time to first asthma exacerbation were observed. A significant decrease in blood eosinophils in the montelukast and fluticasone group was reported compared to the salmeterol and fluticasone group ($P=0.011$).
Calhoun et al[26] Montelukast 10 mg daily vs fluticasone/ salmeterol 100/50 µg twice daily (administered as a combination entity)	DB, DD, MC, RCT Patients 15-72 years diagnosed with asthma for at least 6 months and had been treated with oral or inhaled β_2-agonists for at least 6 weeks prior to study, FEV_1 values of between 50%-80% of predicted value, and an increase in FEV_1 of at least 12% within 30 minutes of inhaled albuterol	N=423 12 weeks	Primary: Change from baseline in pre-dose FEV_1 values Secondary: Morning and evening PEF values, asthma symptom score, percentage of symptom-free days, β_2-agonist use, percentage of rescue-free days, percent of nights with no asthma-related awakenings, percentage of nights with no asthma-related awakenings in patients with $\geq$2 awakenings per week at baseline, and nights per week with no awakenings	Primary: A statistically significant improvement in the percent change from baseline in FEV_1 in the fluticasone/salmeterol group was observed compared to the montelukast group ($P \leq 0.001$). Secondary: A statistically significant improvement in all secondary endpoints for the fluticasone/salmeterol group was observed compared to the montelukast group ($P \leq 0.001$).
Maspero et al[27] Montelukast 5 mg daily	DB, DD, MC, PG, RCT Patients 6-14 years old, with a diagnosis of	N=548 12 weeks	Primary: Morning PEF values	Primary: The mean change from baseline in morning PEF values was 45.8 L/min in the fluticasone/salmeterol group, and 28.7 L/min in the montelukast group ($P<0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone/ salmeterol 100/50 µg twice daily (administered as a combination entity)	asthma for ≥6 months, a FEV_1 between 55%-80% of predicated normal, and ≥12% FEV_1 reversibility, and were not on any asthma control medications except for a SABA		Secondary: FEV_1, evening PEF values, levels of symptoms and rescue medications, assessment of asthma control, asthma exacerbations, and safety	Secondary: The mean change from baseline in evening PEF values was 46.2 L/min in the fluticasone/salmeterol group, and 28.0 L/min in the montelukast group (*P*<0.001). The mean change from baseline in FEV_1 values 0.47 L in the fluticasone/salmeterol group, and 0.30 L in the montelukast group (*P*<0.001). The fluticasone/salmeterol group had significantly greater improvements in percentage of symptom free (*P*=0.025) and rescue free (*P*<0.001) 24-hour periods compared with the montelukast group. Asthma control was higher in the fluticasone/salmeterol group (88.3%) than in the montelukast group (66.7%; *P*<0.001). Twice as many patients in the montelukast group (23.2%) had asthma exacerbations than in the fluticasone/salmeterol group (10.3%). 55% of patients in the fluticasone/salmeterol group and 57% in the montelukast group reported an adverse event during treatment. The most common adverse event reported in both groups was headache (23% salmeterol and fluticasone group, and 27% in the montelukast group).
Sorkness et al[28] Montelukast 5 mg every night at bedtime vs fluticasone 100 µg twice a day vs	DB, RCT Children ages 6 to 14 years old with mild-moderate persistent asthma, with an FEV_1 of ≥80% predicted normal at screening and ≥70% predicted normal at randomization	N=285 48 weeks	Primary: The percent of asthma control days Secondary: Percent of episode-free days, time to first exacerbation requiring prednisone, time to treatment failure, number of treatment failures, ACQ score,	Primary: The percent of asthma control days were 64.2% for the fluticasone monotherapy treatment group, 59.6% for the fluticasone plus salmeterol group, and 52.5% for the montelukast group. The difference between the fluticasone monotherapy and the montelukast group was significant (*P*=0.004). The difference between the fluticasone plus salmeterol group and montelukast was not significant (*P*=0.08). Secondary: The percent of episode-free days were 26.4% in the fluticasone group, 26.8% in the fluticasone plus salmeterol group, and 17.8% in the montelukast group. The differences were significant between the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone/ salmeterol 100/50 µg every morning (administered as a combination entity) and salmeterol 50 µg every night at bedtime vs placebo All patients enrolled in a 2 to 4 week run-in period where they received only albuterol vai an inhaler.			FEV_1%, FEV_1/FVC, morning and evening PEF, and growth	fluticasone group and the montelukast group *(P*=0.040), and between the fluticasone plus salmeterol and montelukast (*P*=0.032). Kaplan-Meier survival curves showed significant superiority of fluticasone compared with montelukast monotherapies in favor of fluticasone in both time to first exacerbation requiring prednisone (*P*=0.002) and time to treatment failure (*P*=0.015). 28 total treatment failures occurred, 5 with fluticasone, 8 with fluticasone plus salmeterol, and 15 with montelukast. The difference between fluticasone monotherapy and montelukast was significant (*P*=0.04). ACQ score improved by -0.69 in the fluticasone monotherapy group, -0.55 in the fluticasone plus salmeterol group, and by -0.45 in the montelukast group. There was no significant difference between the fluticasone monotherapy and fluticasone plus salmeterol therapy in ACQ score improvement, however the difference between fluticasone monotherapy and montelukast was significant (*P*=0.018*).* The mean change in FEV_1 was 6.32% with fluticasone monotherapy, 3.62% with fluticasone plus salmeterol, and -0.58% in the montelukast group. The differences were significant between both the fluticasone monotherapy (*P*<0.001) and fluticasone plus salmeterol (*P*=0.010) therapy when compared to montelukast. The mean change for FEV_1/FVC was 3.95% for the fluticasone monotherapy group, 1.76% for the fluticasone plus salmeterol group, and 0.07% for the montelukast group. The difference was significant between the fluticasone monotherapy group and montelukast (*P*<0.001). Morning PEF values improved by 5.18% in the fluticasone monotherapy group, 5.33% in the fluticasone plus salmeterol group, and by 0.65% in the montelukast group. The differences were significant between both the fluticasone monotherapy (*P*=0.002) and fluticasone plus salmeterol (*P*=0.001) therapy when compared to montelukast.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Evening PEF values improved by 2.95% in the fluticasone monotherapy group, 4.31% in the fluticasone plus salmeterol group, and worsened by -0.57% in the montelukast group. The differences were significant between both the fluticasone monotherapy (*P*=0.017) and fluticasone plus salmeterol (*P*<0.001) therapy when compared to montelukast. The mean increase height from baseline was 5.3 cm with fluticasone monotherapy and fluticasone plus salmeterol. The increase in height was 5.7 cm in the montelukast group however the differences did not reach significance (*P*<0.001) for both groups compared to montelukast.
Busse et al[30] Zafirlukast 20 mg twice a day vs salmeterol xinafoate 42 µg twice a day	DB, DD, MC, PG, RCT Patients 12-73 years with a diagnosis of asthma for at least 6 months; after the run-in period, patients were required to have FEV_1 values of 50%-70% predicted value with or without symptoms, or FEV_1 values of 70.1%-80% predicted value with one or more of the following criteria: average of ≥4 puffs per day of albuterol, symptom score ≥2 in any asthma symptom category on ≥2 days, ≥1 nighttime awakening due to asthma, or ≥2 days when evening to morning PEF values differed by ≥20%	N=289 4 weeks	Primary: Morning PEF values Secondary: Evening PEF values, asthma symptom scores, supplemental albuterol use, nighttime awakenings, FEV_1, and asthma exacerbations	Primary: A statistically significant improvement in morning PEF values in the salmeterol group was reported compared to the zafirlukast group (*P*=0.001). Secondary: A statistically significant improvement in evening PEF values in the salmeterol group was reported compared to the zafirlukast group (*P*=0.019). Statistically significant improvements in asthma symptom scores in the salmeterol group were reported compared to the zafirlukast group (*P*≤0.026). A statistically significant decrease in daytime and nighttime supplemental albuterol use in the salmeterol group was noted compared to the zafirlukast group (*P*=0.004 and *P*=0.013 respectively). No statistically significant difference in nighttime awakenings between the 2 groups was reported (*P*=0.142). A statistically significant improvement in FEV_1 compared to baseline in both groups was reported (*P*<0.001), but no statistically significant difference between groups at the end of the treatment period was observed (*P*=0.293).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Seven patients in the salmeterol group and 9 patients in the zafirlukast group experienced asthma exacerbations during the treatment period (*P* values not reported).
Allergic Rhinitis				
Pullerits et al[31] Montelukast 10 mg daily vs fluticasone propionate nasal spray 200 µg daily vs montelukast 10 mg daily and loratadine 10 mg daily (administered as separate entities) vs placebo	DB, DD, PC, PG, RCT Patients 15-50 years with a diagnosis of allergic rhinitis during the grass pollen season for at least the 2 previous years	N=62 50 days	Primary: Daytime and nighttime nasal symptom score as reported by patient (analysis divided into 3 periods: weeks 1-2 [period 1], weeks 3-5 [period 2], and week 6 to end of study [period 3]) Secondary: EG^{2+} eosinophilic inflammation	Primary: No statistically significant differences were noted in any of the primary endpoints between montelukast monotherapy and placebo. A significant decrease in the development of nasal allergy symptoms in both the fluticasone and the montelukast plus loratadine groups compared to placebo during all 3 treatment periods for daytime symptoms was reported (fluticasone; *P*=0.003, montelukast plus loratadine; *P*=0.04) for period 1 (fluticasone; *P*=0.001, montelukast plus loratadine; *P*=0.04) for period 2 (fluticasone; *P*<0.001, montelukast plus loratadine; *P*<0.001) for period 3. No statistically significant differences in the fluticasone group and the montelukast plus loratadine group in daytime nasal symptom scores were reported. A statistically significant decrease in development of nasal symptoms in the fluticasone group was reported compared to the montelukast monotherapy group (*P*=0.046). A statistically significant decrease in the development of nasal symptoms in the montelukast monotherapy group was observed compared to the placebo group (*P*=0.03). Significantly lower symptom scores in the fluticasone group was observed compared to the placebo group in all periods (*P*=0.02, *P*=0.002, and *P*<0.001 respectively). Significantly lower symptom scores in the fluticasone group were reported compared with the montelukast plus loratadine group during peak season in period 2 (*P*=0.04).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Significantly lower symptom scores in the fluticasone group compared to the montelukast monotherapy group during periods 2 and 3 were observed (P=0.01). Significantly lower symptom scores in the montelukast plus loratadine group compared to the placebo during period 3 were reported (P=0.02). Secondary: A statistically significant increase in EG^{2+} eosinophils in the placebo, montelukast monotherapy, and montelukast plus loratadine groups was observed (P<0.01 for all groups). There was no significant increase in EG^{2+} eosinophils in the fluticasone group (P=0.2).
Baena-Cagnani et al[32] Montelukast 10 mg daily vs desloratadine 5 mg daily vs placebo	DB, PC, RCT Patients 15-75 years diagnosed with seasonal allergic rhinitis for at least 2 years with increased asthma symptoms during the autumn allergy season, clinical symptoms of seasonal allergic rhinitis at screening, FEV_1 ≥70% predicted value, asthma controlled with as-needed bronchodilators only, increase in FEV_1 of at least 12% following bronchodilator use, greater than weekly but no daily asthma	N=924 4 weeks	Primary: Total asthma symptom score, individual asthma symptom scores, FEV_1, PEF values, and use of β_2-agonists Secondary: Not reported	Primary: A statistically significant reduction in the total asthma symptom scores in both the montelukast and desloratadine groups compared with placebo was observed (P≤0.05). No statistically significant differences between montelukast and desloratadine group were noted at any time during the study for total asthma symptom scores. A statistically significant reduction in individual symptom scores in both the montelukast and desloratadine groups compared to placebo was reported (P<0.05). No statistically significant differences between montelukast and desloratadine group were noted at any time during the study for individual asthma symptom scores. A statistically significant increase in FEV_1 in both the montelukast and desloratadine groups was reported compared to placebo (P<0.01 and P<0.05 respectively). There was no statistically significant difference between the montelukast

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	symptoms and/or bronchodilator use, positive skin test for seasonal allergen			and desloratadine groups at any time. Secondary: Not reported
Saengpanich et al[33] Montelukast 10 mg daily and loratadine 10 mg daily (administered as separate entities) vs fluticasone propionate nasal spray 200 µg daily	DB, DD, PG, RCT Patients 21-54 years old with history of sensitivity to ragweed pollen for last 2 years, and had a positive skin test to ragweed pollen	N=63 2 weeks	Primary: Rhino-conjunctivitis Quality of Life Questionnaire, daily nasal symptom scores, number of eosinophils, and level of ECP found in nasal lavage fluids Secondary: Not reported	Primary: A statistically significant improvement in questionnaire answers in both the fluticasone and montelukast plus loratadine groups was observed (P<0.01). A statistically significant reduction in nasal symptoms on the questionnaire in the fluticasone group compared to montelukast plus loratadine group was observed (P=0.05). There was no statistically significant decrease in daily nasal symptom scores in either the fluticasone or montelukast plus loratadine groups, though both did decrease from baseline. There was a statistically significant decrease in number of eosinophils in nasal lavage in the fluticasone group compared to baseline (P=0.05), though no significant decrease in the montelukast plus loratadine group compared to baseline. When compared between groups, this was not statistically significant. A statistically significant decrease in ECP from baseline (P=0.009) and between groups (P=0.04) favoring fluticasone was observed. Secondary: Not reported
Meltzer et al[34] Montelukast 10 mg daily vs montelukast 20 mg	DB, MC, PC, PG, RCT Patients 15-75 years old diagnosed with spring seasonal allergic rhinitis for 2 years, positive skin test for at least 1 of 8 allergens	N=460 2 weeks	Primary: Daytime nasal symptoms score Secondary: Eye symptoms, nighttime symptoms, individual daytime	Primary: A statistically significant improvement in daytime nasal symptom scores in the montelukast plus loratadine group compared to placebo and to either agent alone was observed (P<0.001). A statistically significant improvement in all secondary endpoints in the montelukast plus loratadine group was reported compared to placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily vs loratadine 10 mg daily vs montelukast 10 mg daily and loratadine 10 mg daily (administered as separate entities) vs placebo	including oak, grass, elm, olive, walnut, and sycamore		symptoms, global evaluations, and rhinoconjunctivitis quality of life scores	There was no statistically significant difference in the primary endpoint between montelukast or loratadine monotherapy groups compared to placebo. Secondary: A statistically significant improvement in rhinoconjunctivitis quality of life was reported in the montelukast 10 mg and loratadine group compared to placebo (P<0.05). A statistically significant improvement in daytime eye symptom score, nighttime symptom score, and composite daytime and nighttime symptom score was reported in the montelukast 10 mg monotherapy group compared to placebo (P<0.05).
Mucha et al[35] Montelukast 10 mg daily vs pseudoephedrine 240 mg daily	DB, PG, RCT Patients 18-45 years old with a diagnosis of allergic rhinitis during the ragweed season and a positive skin test to ragweed antigen extract	N=58 2 weeks	Primary: Nasal symptoms, NPIF, quality of life scores, and tolerability profiles Secondary: Not reported	Primary: A statistically significant improvement in all primary outcome measures in both groups compared to baseline values (P<0.05) was observed. A statistically significant improvement in nasal congestion in the pseudoephedrine group was reported compared to the montelukast group (P=0.01). Secondary: Not reported

Study abbreviations: AC=active control, DB=double-blind, DD=double-dummy, MC=multi-center, NI=non-inferiority, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover

Miscellaneous abbreviations: ACQ=Asthma Control Questioner, ALT=alanine aminotransferase, CR=controlled release ECP=eosinophil cationic protein, EG2+=mediator released by eosinophils in response to stimuli, $FEF_{25\%-75\%}$=forced mid-expiratory flow, FEV1=forced expiratory flow in 1 second, FVC=forced vital capacity, ICS=inhaled corticosteroid, IR=immediate release, LABA=long acting beta agonist, LTM=leukotriene modifier, NPIF=nasal peak inspiratory flow, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, SABA=short acting beta agonist, ULN=upper limit of normal

Special Populations

Table 5. Special Populations[1,2,4,5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Montelukast	No dosage adjustment required, in the elderly population. Dosage adjustment required in the pediatric population. Approved for use in children ages 12 months and older for asthma, 15 years and older for exercise induced bronchospams, 2 years and older for seasonal allergic rhinitis, and 6 months and older for perennial allergic rhinitis.	No dosage adjustment required.	No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. Not studied in severe hepatic impairment or in hepatitis.	B	Infant risk cannot be ruled out.
Zafirlukast	No dosage adjustment required, in the elderly population. Dosage adjustment required in the pediatric population. Approved for use in children ages 5 and older.	No dosage adjustment required.	No dosage adjustment required.	B	Infant risk cannot be ruled out.
Zileuton	No dosage adjustment required in the elderly population. No dosage adjustment required in the pediatric population. Approved for use in children ages 12 and older.	No dosage adjustment required.	Contraindicated in patients with active liver disease and in patients with elevated hepatic function enzymes ≥3 times the upper limit of normal.	C	Infant risk cannot be ruled out.

Adverse Drug Events

The majority of adverse events associated with these agents are similar to placebo. For montelukast the most common adverse events were headache, influenza, abdominal pain, cough, dyspepsia, and upper respiratory infection. With zafirlukast the most common adverse reactions were headache, infection, nausea, and diarrhea; for zileuton the most common adverse events were sinusitis, nausea, and pharyngolaryngeal pain.

Table 6. Adverse Drug Events[1,2,4,5,36]

Adverse Event(s)	Montelukast	Zafirlukast	Zileuton
Central Nervous System			
Dizziness	1.9	1.6	-
Headache	18.4	13	23
Dermatological			
Rash	1.6	✔	>1
Urticaria	≥2	-	3.3
Gastrointestinal			
Abdominal pain	2.9	1.8	4.8
Diarrhea	≥2	2.8	5
Dyspepsia	2.1	1.3	8.2
Gastroenteritis	1.5	-	-
Nausea	≥2	3.1	5
Vomiting	≥2	1.5	>1
Hematologic			
Decreased white blood cell count	-	-	2.6
Vasculitis (consistent with Churg-Strauss syndrome)	✔	✔	-
Laboratory Test Abnormalities			
Alanine aminotransferase elevations	2.1	1.5	1.8-3.2
Aspartate aminotransferase elevations	1.6	-	-
Musculoskeletal			
Back pain	-	1.5	-
Myalgia	-	1.6	7
Respiratory			
Bronchitis (acute)	≥2	-	-
Cough	2.7	-	-
Influenza	≥2	-	-
Laryngitis	≥2	-	-
Nasal congestion	1.6	-	-
Pharyngitis	≥2	-	5
Pneumonia	≥2	-	-
Rhinitis (infective)	≥2	-	-
Rhinorrhea	≥2	-	-
Sinusitis	≥2	-	6.5
Upper respiratory infection	≥2	-	9
Wheezing	≥2	-	-
Other			
Asthenia	1.8	1.8	3.8
Conjunctivitis	≥2	-	>1%
Ear pain	≥2	-	-
Fever	1.9	1.6	>1
Infection	-	3.5	-
Otitis media	≥2	-	-
Pain (dental)	1.7	-	-
Pain (generalized)	-	1.9	-
Tonsillitis	≥2	-	-
Tooth infection	≥2	-	-

- Event not reported or incidence <1%.
✔ Percent not specified.

Contraindications / Precautions

Montelukast, zafirlukast, and zileuton are contraindicated in patients with hypersensitivity to any of the compounds that make up the respective medications. Zileuton is additionally contraindicated in patients with active liver disease or with hepatic function enzyme levels greater than or equal to three times the upper limit of normal. All three medications should not be used for the reversal of bronchospams in acute asthma attacks, or in status asthmaticus. The agents can be continued during acute exacerbations of asthma.[1,2,4]

Montelukast therapy has additionally been linked to suicidal ideation and behavior, includeding suicide, in post-marketing reports. In March 2008 the Food and Drug Administration (FDA) began compiling data from all three leukotriene modifying agents regarding this safety issue. As of January 2009, the data evaluated showed that the leukotriene modifiers (LTM) do not appear to have an association with either suicide or suicidal behavior. Data continues to be reviewed however and no definitive conclusion regarding these agents and their potential to cause other psychiatric problems, such as mood and behavioral changes, has been reached by the FDA.[7]

Although the dose of an inhaled corticosteroid (ICSs) can be gradually reduced while on concurrent montelukast therapy, montelukast should not be abruptly substituted in place of inhaled or oral corticosteroids.[1] It is also not recommended to decrease the dose or stop the use of antiasthma medications while being treated with zafirlukast.[2]

Caution is also advised for patients being treated with montelukast who also have a concurrent aspirin allergy, as montelukast is not indicated for bronchospam reversal in these patients or in Non-steroidal anti-inflammatory drug (NSAID)-related sensitivities. Patients being treated with the chewable montelukast tablets should also be advised that they contain phenylketonurics.[1]

Additionally, caution is advised in patients who are concurrently being treated with both zafirlukast and warfarin. The concomitant use of these two agents results in a clinically significant increase in prothrombin time (PT). Patients should have their PT monitored closely and their warfarin dose should be adjusted accordingly.[2]

Patients being treated for asthma with montelukast or zafirlukast may, in rare instances, present with systemic eosinophilia. Clinical features of the eosinophilia, such as vasculitis, can be consistent with Churg-Strauss syndrome. Health care providers should be alert to the presentation of eosinophilia, vasculitic rash, worsening of pulmonary symptoms, cardiac complications, and neuropathy in patients.[1,2]

Zafirlukast therapy, at recommended doses, has been linked to reports of life-threatening hepatic failure. In most patients the liver enzyme values returned to normal upon discontinuation of the medication; however in some rare instances there was progression to fulminant hepatitis, and subsequently to hepatic failure, liver transplantation, and death. Although periodic serum transaminase exams have not been proven to prevent serious adverse events it is generally assumed that earlier detection of any medication-induced hepatic injury along with the immediate discontinuation of the medication can increase the possibility of recovery.[2]

Zileuton therapy also has the potential to cause elevations in one or more hepatic function enzymes, as well as bilirubin. These laboratory values can potentially remain unchanged, completely resolve, or progress to significant hepatic injury. The alanine aminotransferase (ALT) test is the most sensitive indicator of liver injury. Hepatic function enzymes should be assessed prior to initiating zileuton therapy, once a month for three months while being treated with the medication, every two to three months for the remainder of the first year, and periodically thereafter in long-term therapy. If the transaminase levels are elevated five times or greater above the upper limit of normal, or signs and symptoms of liver dysfunction develop the medication should be immediately discontinued. Due to the effect that zileuton has on the hepatic system, further caution should be used in patients who consume large quantities of alcohol or in those with a past history of liver disease.[4]

Montelukast has been associated with rare post-marketing reports of liver injury and cholestatic hepatitis, though most occurred in patient with other underlying risk factors for the development of liver injury including other medications and underlying liver disease. Elevations in liver transaminase levels were not different than placebo.[1] Montelukast is the only agent of the three LTM that does not include a specific warning in its label regarding severe hepatotoxicity or death due to hepatic failure.[2-4]

Drug Interactions

Table 7. Drug Interactions[1,2,4-6]

Generic Name	Interacting Medication or Disease	Potential Result
Zafirlukast, Zileuton	Warfarin	Concurrent use can result in clinically significant increases in prothrombin time. Close monitoring of prothrombin time in patients on both medications is recommended.
Zafirlukast	Theophylline	Concurrent use of zafirlukast and theophylline may result in decreased mean plasma levels of zafirlukast.
Zileuton	Theophylline	Zileuton may decrease the metabolism of theophylline compounds, and thereby increase theophylline levels. When starting zileuton, it may be necessary to decrease the dose of theophylline by 50%.
Zileuton	Pimozide	Zileuton may inhibit the metabolism of pimozide (possibly via CYP 450 3A4 enzyme), potentially causing fatal cardiac arrhythmias. Concurrent use is considered a contraindication.

Dosage and Administration

Table 8. Dosing and Administration[1,2,4,5]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Montelukast	Asthma: Tablet: Initial, 10 mg daily in the evening; maintenance, same as initial Exercise-induced bronchoconstriction (EIB): Tablet: 10 mg at least 2 hours prior to exercise; additional doses should not be administered within 24 hours Seasonal and perennial allergic rhinitis: Tablet: Initial, 10 mg daily at any time of day; maintenance, same as initial	Perennial allergic rhinitis: Oral granules: 6-23 months of age, initial, 4 mg once daily; maintenance, same as initial Asthma: Oral granules: 12-23 months of age, initial, 4 mg once daily; maintenance, same as initial Asthma, seasonal and perennial allergic rhinitis: Chewable tablet or oral granules: 2-5 years of age, initial, 4 mg daily in the evening; maintenance, same as initial Asthma, seasonal and perennial allergic rhinitis: Chewable tablet: 16-14 years of age, initial, 5 mg daily in the evening; maintenance, same as initial	Chewable tablet: 4 mg 5 mg Oral granules: 4 mg Tablet: 10 mg
Zafirlukast	Asthma: Tablet: initial, 20 mg twice daily within 1 hour before or 2 hours after meals; maintenance, same as initial	Asthma: Tablet: 5-11 years of age, initial, 10 mg twice daily; maintenance, same as initial	Tablet: 10 mg 20 mg

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Zileuton	Asthma: Extended release tablet: Initial, 1,200 mg twice daily within 1 hour after morning and evening meals; maintenance: same as initial	Same dosing recommendations as adults for children aged 12 years and older.	Extended release tablet: 600 mg

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guidelines	Recommendations
The National Heart, Lung, and Blood Institute (NHLBI)/ National Asthma Education and Prevention Program (NAEPP): **Guidelines for the Diagnosis and Management of Asthma (2007)**[8]	Diagnosis • To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction, and alternate diagnoses must be excluded. • The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility, and additional studies to exclude alternate diagnoses. • A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections, and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as additional pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing, and biomarkers of inflammation may be useful when considering alternative diagnoses. Treatment • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction. • For initiating treatment, asthma severity should be classified, and the initial treatment should correspond to the appropriate severity category. • Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. • Quick relief medications include short-acting β_2-agonists (SABAs), anticholinergics, and systemic corticosteroids. Long-term Control Medications • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. • When patients ≥12 years of age require more than low-dose ICSs, the addition of a long-acting β_2-agonist (LABA) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
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antagonists (LTRAs), theophylline, or in adults, zileuton.
• Mast cell stabilizers (cromolyn and nedocromil) are alternatives for the treatment of mild persistent asthma. They can also be used as preventative treatment prior to exercise or unavoidable exposure to known allergens.
• Omalizumab, an immunomodulator, is adjunctive therapy in patients ≥12 years old with allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy.
• LTRAs (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma.
• LABAs (salmeterol and formoterol) are not to be used as monotherapy for long-term control of persistent asthma.
• LABAs should continue to be considered for adjunctive therapy in patients ≥5 years of age who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA.
• Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.
• Tiotropium bromide is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease and has not been studied in the long-term management of asthma.

Quick-relief Medications
• SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise induced bronchospasm.
• There is inconsistent data regarding the superior efficacy of levalbuterol over albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol.
• Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations.
• Systemic corticosteroids are used for moderate/severe exacerbations as adjunct to SABAs to speed recovery and prevent exacerbations.
• The use of LABAs is not currently recommended to treat acute symptoms or exacerbations of asthma.

Assessment, Treatment, and Monitoring
• A stepwise approach to managing asthma is recommended to gain and maintain control of asthma in both the impairment and risk domains.
• Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased use or SABA use >2 days a week for symptom relief generally indicates inadequate asthma control.
• The stepwise approach for managing asthma is outlined below:
<table>
<tr><th>Intermittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td>Preferred
SABA as needed</td><td>Preferred
Low-dose ICS

Alternative
Cromolyn, LTRA, nedocromil, or theophylline</td><td>Preferred
Low-dose ICS+LABA OR medium-dose ICS

Alternative
Low-dose ICS+either a LTRA,</td><td>Preferred
Medium-dose ICS+LABA

Alternative
Medium-dose ICS+either a LTRA,</td><td>Preferred
High-dose ICS+LABA AND consider omalizumab for patients who have allergies</td><td>Preferred
High-dose ICS+LABA+ oral steroid AND consider omalizumab for patients who have allergies</td></tr>
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</td></tr>
</table>

Clinical Guidelines	Recommendations
	<table><tr><td></td><td></td><td>theophylline, or zileuton</td><td>theophylline, or zileuton</td><td></td><td></td></tr></table> Management of Exacerbations • Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended. Special Populations • For exercise induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. LTRAs may also attenuate exercise induced bronchospasm and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention however they are not as effective as SABAs. The addition of cromolyn to a SABA is helpful in some individuals who have exercise induced bronchospasm. • Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery. • Albuterol is the preferred SABA in pregnancy because of an excellent safety profile. • ICSs are the preferred treatment for long-term control medication in pregnancy. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention (2008)**[9]	Diagnosis • A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness. • Measurements of lung function (spirometry or peak expiratory flow) provide an assessment of the severity of airflow limitation, its reversibility, and its variability and provide confirmation of the diagnosis of asthma. Treatment • Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages. • Measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible. • Controller medications are administered daily on a long-term basis and include inhaled and systemic glucocorticosteroids, leukotriene modifiers, LABAs in combination with inhaled glucocorticosteroids, sustained-released theophylline, cromones, and anti-immunoglobulin E (IgE). • Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline, and SABAs. Controller Medications • Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. • Inhaled glucocorticosteroids differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences. • To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids. • Leukotriene modifiers are generally less effective than inhaled

Clinical Guidelines	Recommendations
	glucocorticosteroids therefore may be used as an alternative treatment in patients with mild persistent asthma. • Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. • Leukotriene modifiers used as add-on therapy may reduce the dose of inhaled glucocorticosteroids required by patients with moderate to severe asthma, and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids. • Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy. • LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. • When a medium dose of an inhaled glucocorticosteroid fails to achieve control, the addition of a LABA is the preferred treatment. • Controlled studies have shown that delivering a LABA and an inhaled glucocorticosteroid in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance, and ensure that the LABA is always accompanied by a glucocorticosteroid. • Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance, this use is not approved by the Food and Drug Administration (FDA). • Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on inhaled glucocorticosteroids alone. • Cromolyn and nedocromil are less effective than a low dose of an inhaled glucocorticosteroid. • Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed. • Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE. • Long-term oral glucocorticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects. • Other anti-allergic compounds have limited effect in the management of asthma. <u>Reliever Medications</u> • Rapid-acting inhaled β_2-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise-induced bronchoconstriction, in patients of all ages. • Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required. • Although the guidelines states that formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with inhaled glucocorticosteroids, the use of this agent as a rescue inhaler is not approved by the FDA. • Ipratropium bromide, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists. • Short-acting theophylline may be considered for relief of asthma symptoms. • Short-acting oral β_2-agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication however they are

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
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associated with a higher prevalence of adverse effects.
• Systemic glucocorticosteroids are important in the treatment of severe acute exacerbations.

<u>Assessment, Treatment, and Monitoring</u>
• The goal of asthma treatment is to achieve and maintain clinical control.
• To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled.
• Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.
• Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates need to reassess treatment.
• The management approach based on control is outlined below:
<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Asthma education and environmental control</td></tr>
<tr><td colspan="5">As needed rapid-acting β_2-agonist</td></tr>
<tr><td rowspan="5">Controller options</td><td>Select one</td><td>Select one</td><td>Add one or more</td><td>Add one or both</td></tr>
<tr><td>Low-dose inhaled glucocortico-steroid</td><td>Low-dose inhaled glucocorticosteroid +LABA</td><td>Medium- or high-dose inhaled glucocortico-steroid+LABA</td><td>Oral glucocortico-steroid</td></tr>
<tr><td>Leukotriene modifier</td><td>Medium- or high-dose inhaled glucocorticosteroid</td><td>Leukotriene modifier</td><td>Anti-IgE treatment</td></tr>
<tr><td>-</td><td>Low-dose inhaled glucocorticosteroids +leukotriene modifier</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td>Low-dose inhaled glucocorticosteroid +sustained-release theophylline</td><td>-</td><td>-</td></tr>
</table>

<u>Management of exacerbations</u>
• Repeated administration of rapid-acting inhaled β_2-agonists is the best method of achieving relief for mile to moderate exacerbations.
• Systemic glucocorticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled β_2-agonists or if the episode is severe.
<u>Special Populations</u>
• LABAs may also be used to prevent exercise induced bronchospasm and because of a more rapid onset of action, formoterol is more suitable for symptom relief as well as symptom prevention over salmeterol.
• Appropriately monitored use of theophylline, inhaled glucocorticosteroids, β_2-agonists, and leukotriene modifiers, specifically montelukast, are not associated with an increased incidence of fetal abnormalities.
• Inhaled glucocorticosteroids have been shown to prevent exacerbations of asthma during pregnancy.
• Acute exacerbations during pregnancy should be treated with nebulized rapid-acting β_2-agonists and oxygen. Systemic glucocorticosteroids should be instituted when necessary.
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Clinical Guidelines	Recommendations
Joint Task Force on Practice Parameters for Allergy and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[10]	Diagnosis • An effective evaluation of a patient with rhinitis includes a determination of the pattern, chronicity, and seasonality of nasal and related symptoms; response to medications; presence of coexisting conditions; occupational exposure; and a detailed environmental history and identification of precipitating factors. • A physical examination with emphasis on the upper respiratory tract should be performed in patients with a history of rhinitis. • Skin testing is the preferred test for the diagnosis of IgE-mediated sensitivity and is indicated to provide evidence of allergic basis for the causes of the patient's symptoms. • Nasal smears for eosinophils are not necessary for routine use in diagnosing allergic rhinitis but may be useful when the diagnosis of allergic rhinitis is in question. • The measurement of total IgE should not be routinely performed. • Cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, and hair analysis are not recommended diagnostic procedures. Treatment • The management and monitoring of rhinitis should be individualized and based on symptoms, physical examination findings, comorbidities, patient age and patient preferences. • Environmental control measures include avoidance of known allergic triggers when possible. • The available second-generation oral antihistamines, which are generally preferred over first-generation antihistamines, appear to be equally effective in the treatment of allergic rhinitis. • Concerning the second generation antihistamines, fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • Intranasal antihistamines are efficacious and equal to or superior to oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines may be considered for use as first-line treatment for the treatment of allergic and nonallergic rhinitis. • Leukotriene receptor antagonists alone or in combination with antihistamines are effective in the treatment of allergic rhinitis. • Topical decongestants are not recommended for regular daily use but can be considered for short-term management of nasal congestion. • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis and all are considered equally efficacious. • Intranasal corticosteroids can provide significant relief of symptoms when used on a regular basis as well as an as-needed basis. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • A short course of oral corticosteroids may be appropriate for very severe or intractable nasal symptoms or significant nasal polyposis. • Intranasal cromolyn sodium may be effective for the prevention and treatment of allergic rhinitis.

Clinical Guidelines	Recommendations
	• Intranasal anticholinergics may be effective in reducing rhinorrhea and are more effective when used in combination with intranasal corticosteroids. • Allergen immunotherapy is effective and should be considered for patients with allergic rhinitis who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. • Surgery may be indicated in the management rhinitis.
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Treatment of Respiratory Illness in Children and Adults (2008)**[11]	Diagnosis • Patients can present with any of the following symptoms: congestion, rhinorrhea, pruritus, sneezing, posterior nasal discharge, and sinus pressure/pain. • A past medical history of facial trauma or surgery, asthma, rhinitis, atopic dermatitis, or thyroid disease may be suggestive of a rhinitis. In addition, a family history of atopy or other allergy associated conditions make allergic rhinitis more likely. • The most common physical findings suggestive of rhinitis tend to be swollen nasal turbinates, rhinorrhea and pruritus however allergic conjunctivitis may also be present. • Symptoms suggestive of allergic or episodic rhinitis include sneezing, itching of the nose, palate or eyes, and clear rhinorrhea. Nasal congestion is more commonly associated with perennial rhinitis. • Diagnostic testing should be considered if the results would change management. • Skin tests and radioallergosorbent tests identify the presence of IgE antibody to a specific allergen and are used to differentiate allergic from nonallergic rhinitis and to identify specific allergens causing allergic rhinitis. • A nasal smear for eosinophils cannot differentiate allergic from nonallergic rhinitis. The test is a good predictor of a patient's response to treatment topical nasal corticosteroids. • Peripheral blood eosinophil count, total serum IgE level, Rinkel method of skin titration and sublingual provocation testing are not recommended. Treatment • If a clinical diagnosis is obvious, symptomatic treatment, which consists of education on avoidance and medication therapy, should be initiated. • Avoidance of triggers is recommended. • Intranasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms. • Regular daily use of intranasal corticosteroids is required to achieve optimal results. • Systemic corticosteroids should be reserved for refractory or severe cases of rhinitis. Injectable steroids are not generally recommended. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis except nasal congestion. • Antihistamines are somewhat less effective than intranasal corticosteroids however oral antihistamines are an effective alternative in patients who cannot use or prefer not to use intranasal corticosteroids. They also can be added as adjunctive therapy to intranasal corticosteroids. • Second-generation antihistamines are recommended because they are less sedating and cause less central nervous system impairment. • Leukotriene inhibitors are as effective as second-generation antihistamines for the treatment of allergic rhinitis however are not as effective as

Clinical Guidelines	Recommendations
	intranasal corticosteroids. • Oral decongestants are effective in reducing nasal congestion. • Topical decongestants, which have the potential to induce rebound congestion after 3 days, are effective for the short-term relief of nasal congestion. • Cromolyn is most effective when used prior to the onset of allergic symptoms and is a good alternative to corticosteroids however four times daily dosing may cause compliance problems. • Intranasal anticholinergics are effective in relieving anterior rhinorrhea in allergic and nonallergic rhinitis. • Reserve immunotherapy for patients with significant allergic rhinitis in which avoidance activities and pharmacotherapy are insufficient to control symptoms. • If adequate relief is achieved appropriate follow-up should include further education on avoidance activities and medications. • If patients anticipate unavoidable exposure to known allergens they should begin the use of medications prior to exposure. • If adequate relief is not achieved within 2 to 4 weeks consider a trial of another medication, allergen skin testing by a qualified physician, a complete nasal examination, or a diagnosis of nonallergic rhinitis. • Treatment options for nonallergic rhinitis include intranasal corticosteroids, oral decongestants and antihistamines, topical antihistamines, and nasal strips.

Conclusions

The leukotriene modifiers (LTMs) consist of two categories of agents; the leukotriene-receptor antagonists (LTRAs) montelukast and zafirlukast, and the 5-lipoxygenase inhibitor, zileuton. All three agents are Food and Drug Administration (FDA) approved for the chronic treatment and prophylaxis of asthma. Montelukast is additionally indicated for prophylaxis of exercise-induced bronchoconstriction as well as for the treatment of symptoms in both seasonal and perennial allergic rhinitis.[1,2,4]

Current treatment guidelines recommend the use of LTMs as one of the treatment alternatives to low-dose inhaled corticosteroids (ICSs) in patients with mild persistent asthma. These agents can also be considered as alternative adjunctive therapy in patients not achieving adequate symptom control with an ICS, as monotherapy or in combination with a long-acting β_2-agonist (LABA). The allergic rhinitis guidelines consider intranasal corticosteroids to be first-line treatment for the management of allergic rhinitis and that the LTM can be considered second-line agents along with antihistamine agents. It should also be noted that none of the current guidelines give preference to one LTM over another.[8-11]

There are no head-to-head trials directly comparing the efficacy and safety of the LTMs to each other for any indication. In placebo controlled trials the LTMs demonstrated efficacy in most aspects of asthma control. However when compared to other long-term control medications, such as ICSs and LABAs, the LTMs were unable to demonstrated equivalence or significant advantages in clinical outcomes. In regards to safety, postmarking data appears to show that both zafirlukast and zileuton have a higher risk of hepatotoxicity than montelukast.[1,2,4,19-33]

With regards to allergic rhinitis, montelukast has been shown to be more effective than placebo, and has demonstrated comparable efficacy to the second-generation antihistamines; however the agent was shown to be less effective than the intranasal corticosteroids.[34-38]

Recommendations

In recognition of the well established role of the leukotriene modifiers for the treatment of asthma and allergic rhinitis, the similar efficacy between all three agents, the higher risk of hepatic toxicity with zileuton, the lack of availability of any agent as a generic entity and cost considerations, no changes are recommended to the current approval criteria.

Accolate® and Singulair® are preferred agents on the OVHA Preferred Drug List (PDL) and are available without a prior authorization.

Zyflo® and Zyflo CR® require prior authorization with the following approval criteria:

- The patient has had a documented side effect, allergy, or treatment failure to Accolate and Singulair.

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